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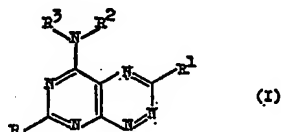
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(54) PYRIMIDOTRIAZINES AND A PROCESS FOR THE  
 MANUFACTURE THEREOF

(71) We, ROCHE PRODUCTS LIMITED, a British Company of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with pyrimidotriazines and a process for the manufacture thereof.

The pyrimidotriazines provided by the present invention have the following general formula



wherein R represents a trifluoromethyl, lower alkyl, aryl or lower aralkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl, aryl or lower aralkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl, hydroxy, hydroxy-(lower alkyl) or acyl group or R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group which may be joined directly or through an oxygen, nitrogen or sulphur atom to form with the nitrogen atom to which they are attached a 5-membered or 6-membered heteromonocyclic ring.

The pyrimidotriazines provided by the present invention possess interesting pharmaco-

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logical activity. In particular they exhibit anti-inflammatory activity while certain of them also possess a diuretic activity.

The term "lower alkyl" is used in this specification to mean both straight-chain and branched chain alkyl groups which contain from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl. The term "lower alkenyl" is used to mean both straight-chain and branched-chain alkenyl groups which contain from 2 to 6 carbon atoms such as vinyl, allyl, and  $\beta$ , $\beta$ -dimethylallyl. The term "lower alkynyl" means both straight-chain and branched-chain alkynyl groups containing from 2 to 6 carbon atoms such as propynyl and butynyl. The term "lower cycloalkyl" means cycloalkyl groups containing from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl and cyclohexyl. The term "aryl" means phenyl and phenyl which carries one or more halo (i.e. fluoro, chloro, bromo or iodo), lower alkyl and/or lower alkoxy substituents. Examples of such substituted-aryl groups are *p*-chloro - phenyl, 3,4 - dichloro - phenyl, *ortho*tolyl, *para*tolyl and *p* - methoxy - phenyl. The term "lower aralkyl" means an aryl-(lower alkyl) group in which the "aryl" and "lower alkyl" moieties are as defined earlier; for example, benzyl, *p* - chloro - benzyl and  $\beta$ -phenethyl. The hydroxy-(lower alkyl) group may be, for example, a 2 - hydroxy - ethyl or 3 - hydroxy - propyl group. The term "acyl" is used to mean an acyl group derived from a lower alkane carboxylic acid (one containing up to 6 carbon atoms such as acetic acid, propionic acid, and butyric acid) or from an aromatic carboxylic acid such as benzoic acid or a substituted-benzoic acid such as

*p* - chloro - benzoic acid. Examples of 5-membered and 6-membered heteromonocyclic rings are the pyrrolidino, piperidino, piperazino, morpholin and thiamorpholino rings.

- 5 One interesting class of pyrimidotriazines of formula I comprises those in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydrogen atom or a lower alkyl group.
- 10 Another interesting class of pyrimidotriazines of formula I comprises those in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group.
- 15 Particularly interesting pyrimidotriazines of formula I are those in which R represents a methyl or ethyl group, R<sup>1</sup> represents a hydrogen atom, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a methyl group or R<sup>2</sup> and R<sup>3</sup> each represent a methyl group.

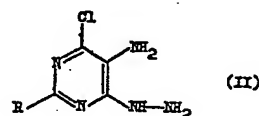
Examples of pyrimidotriazines of formula I are:

- 25 5 - amino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
5 - amino - 3,7 - dimethyl - pyrimido[5,4-e] - as - triazine,  
5 - amino - 7 - ethyl pyrimido[5,4-e] - as - triazine,  
30 5 - amino - 7 - *n* - hexyl - pyrimido[5,4-e] - as - triazine,  
7 - methyl - 5 - methylamino - pyrimido[5,4-e] - as - triazine,  
5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
35 5 - ethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
5 - isopropylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
40 5 - *n* - butylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
5 - diethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
7 - methyl - 5 - morpholino - pyrimido[5,4-e] - as - triazine,  
45 5 - dimethylamino - 7 - neopentyl - pyrimido[5,4-e] - as - triazine,  
5 - methylamino - 7 - neopentyl - pyrimido[5,4-e] - as - triazine,  
50 5 - dimethylamino - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - as - triazine,  
7 - methyl - 5 - methylamino - 3 - phenyl - pyrimido[5,4-e] - as - triazine,  
55 5 - amino - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - as - triazine,  
5 - amino - 7 - ethyl - 3 - phenyl - pyrimido[5,4-e] - as - triazine,  
5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine,  
60 5 - methylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine,  
5 - amino - 7 - phenyl - pyrimido[5,4-e] - as - triazine,

- 5 - amin - 3 - methyl - 7 - phenyl - pyrimido[5,4-e] - as - triazine, 65  
5 - dimethylamino - 7 - trifluoromethyl - pyrimido[5,4-e] - as - triazine,  
5 - methylamino - 7 - trifluoromethyl - pyrimido[5,4-e] - as - triazine,  
5 - amino - 7 - trifluoromethyl - pyrimido[5,4-e] - as - triazine, 70  
5 - allylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
7 - methyl - 5 - propargylamino - pyrimido[5,4-e] - as - triazine, 75  
5 - cyclopropylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
5 - hydroxylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
7 - ethyl - 5 - (2 - hydroxy - ethylamino) - pyrimido[5,4-e] - as - triazine, 80  
5 - acetamido - 7 - methyl - pyrimido[5,4-e] - as - triazine,  
7 - methyl - 5 - propionamido - pyrimido[5,4-e] - as - triazine, 85  
5 - isobutyramido - 7 - methyl - pyrimido[5,4-e] - as - triazine and  
7 - methyl - 5 - (*p* - chloro - benzamido) - pyrimido[5,4-e] - as - triazine.

According to the process provided by the present invention, the pyrimidotriazines of formula I hereinbefore are manufactured by

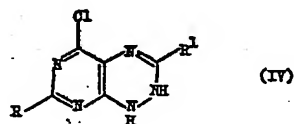
(a) reacting a hydrazinopyrimidine of the general formula



wherein R has the significance given earlier, with a compound of the general formula



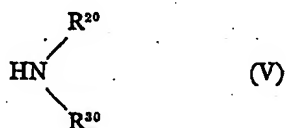
wherein R<sup>1</sup> has the significance given earlier and R<sup>4</sup> represents a lower alkyl group, in the presence of a strong acid to give an acid addition salt of a compound of the general formula



wherein R and R<sup>1</sup> have the significance given earlier, and treating said acid addition salt or the free base obtained therefrom with ammonia under oxidising conditions or with an alkyl metal azide or with ammonia in the presence of an alkali metal azide to give

a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom, or

- (b) reacting an acid addition salt of a compound of formula IV or the free base obtained therefrom with an amine of the general formula



- wherein R<sup>20</sup> represents a hydrogen atom and R<sup>30</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group or R<sup>20</sup> and R<sup>30</sup> each represent a lower alkyl group which may be joined directly or through an oxygen, nitrogen or sulphur atom to form with the nitrogen atom to which they are attached a 5-membered or 6-membered heteromonocyclic ring, under oxidising conditions to give a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> have any of the values accorded to R<sup>20</sup> and R<sup>30</sup> hereinbefore, or

- (c) treating a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group with hydroxylamine to give a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydroxy group, or

- (d) appropriately acylating a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom to give a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents an acyl group, or

- (e) converting a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group into a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group by heating with an amine of the general formula



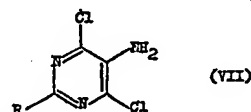
- wherein R<sup>31</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group, or

- (f) converting a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group into a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom by heating with ammonia, or

- (g) treating a pyrimidotriazine of formula

I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom with an amine of formula VI hereinbefore to yield a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group.

The hydrazinopyrimidine starting materials of formula II used in embodiment (a) of the present process can be prepared, for example, by reacting a substituted-pyrimidine of the general formula



wherein R has the significance given earlier, with hydrazine hydrate.

The reaction of a hydrazinopyrimidine of formula II with a compound of formula III is carried out in the presence of a strong acid. Any strong acid may be used, but it is preferred to use a strong inorganic acid such as a hydrohalic acid (e.g. hydrochloric acid) or sulphuric acid. The reaction is conveniently carried out in an inert organic solvent such as a lower alkanol (e.g. methanol or ethanol) or an N,N - di(lower alkyl) - (lower alkanoyl) amide (e.g. N,N - dimethylformamide). Other organic solvents may be used provided that they are inert under the conditions of the reaction. The reaction, which proceeds exothermically, is suitably carried out at a temperature of from 20°C to 30°C, preferably at room temperature.

A resulting acid addition salt of a compound of formula IV or, preferably a free base obtained therefrom is then treated with ammonia under oxidising conditions or an alkali metal azide or ammonia in the presence of an alkali metal azide to give a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom. A free base of formula IV can be obtained from an acid addition salt of a compound of formula IV by, for example, treatment with a base such as an alkali metal bicarbonate (e.g. sodium bicarbonate) or, when R and/or R<sup>3</sup> represents an aryl group, by stirring a mixture of the acid addition salt in water. Of the alkali metal azides which may be used, sodium azide is preferred. This treatment is expediently carried out in an inert organic solvent such as a lower alkanol (e.g. methanol or ethanol), a mixture of a lower alkanol and water or an N,N - di(lower alkyl) - (lower alkanoyl) amide (e.g. N,N - dimethylformamide). Other organic solvents which are inert under the conditions of the treatment may also be employed. The treatment is suitably carried out

at an elevated temperature, preferably at the reflux temperature of the mixture.

In accordance with embodiment (b) of the present process, an acid addition salt of a compound of formula IV or free base obtained therefrom (e.g. in the manner described earlier) is reacted with an amine of formula V under oxidising conditions to give a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> have any of the values accorded to R<sup>20</sup> and R<sup>30</sup> hereinbefore. Examples of amines of formula V which can be used are lower alkyl amines (e.g. methyl amine, and ethyl amine), lower alkenyl amines (e.g. allyl amine), lower alkynyl amines (e.g. propargyl amine), lower cycloalkyl amines (e.g. cyclopropylamine), aryl amines (e.g. aniline, and *p*-chloro - aniline), lower aralkyl amines (e.g. benzyl amine, and *p*-chloro - benzyl amine), hydroxy-(lower alkyl) amines (e.g. ethanolamine), di(lower alkyl) amines (e.g. dimethyl amine, and diethyl amine) and appropriate heterocyclic amines (e.g. morpholine, pyrrolidine, piperazine, piperidine, and thiamorpholine. When an acid addition salt of a compound of formula IV is used, it is preferred to employ at least 3 moles (especially 3—4 moles) of an amine of formula V per mol of said addition salt. This reaction is expediently carried out in an inert polar organic solvent such as a lower alkanol (e.g. methanol or ethanol), acetonitrile or dimethyl sulphoxide. The oxidising conditions may be provided by passing oxygen or air through a mixture of the reactants in a solvent of the kind mentioned earlier or even by stirring the mixture in air. The reaction is suitably carried out at a temperature between 15°C and 25°C, preferably at room temperature.

According to embodiment (c) of the present process, pyrimidotriazines of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydroxy group are manufactured by treating a pyrimidotriazine corresponding to formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group with hydroxylamine. This treatment is suitably carried out in an inert organic solvent (e.g. a lower alkanol such as methanol or ethanol) and at an elevated temperature, preferably at a temperature at or near the reflux temperature of the mixture.

The acylation of a pyrimidotriazine corresponding to formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom in accordance with embodiment (d) of the present process to give a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents an acyl group is carried out according to methods known *per se*. The acylation is, however, preferably carried out using an appropriate acid anhydride (e.g. acetic anhydride, propionic anhydride, and isobutyric anhydride) at an elevated temperature (e.g. a temperature up to the reflux temperature of the mixture). This acylation procedure can be

carried out, if desired, in the presence of an inert organic solvent (e.g. a halogenated hydrocarbon such as chloroform) and a tertiary organic base (e.g. triethylamine or pyridine). Alternatively, the acylation can be carried out using an appropriate acid halide, preferably an acid chloride such as, (for example, acetyl chloride, propionyl chloride, benzoyl chloride, and *p*-chloro - benzoyl chloride). This acylation procedure is suitably carried out at about room temperature in the presence of a tertiary organic base (e.g. triethylamine or, preferably, pyridine).

In accordance with embodiment (e) of the present process, a pyrimidotriazine corresponding to formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group is heated with an amine of formula VI to yield a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group. Examples of amines of formula VI which may be used are lower alkylamines (e.g. methylamine, ethylamine, propylamine, and isopropylamine, lower alkenylamines (e.g. allylamine), lower alkynylamines (e.g. propargylamine), lower cycloalkylamines (e.g. cyclopropylamine, and cyclobutylamine), arylamines (e.g. aniline, and *p*-chloro - aniline), lower aralkylamines (e.g. benzylamine, and *p*-chlorobenzylamine) and lower alkanolamines (e.g. ethanolamine). It is preferred to use at least a part of the amine of formula VI in the form of an acid addition salt, particularly the hydrochloride. It is also convenient to use a large molar excess of the amine of formula VI or acid addition salt thereof. This heating can be carried out in an inert organic solvent, preferably a lower alkanol (e.g. methanol or ethanol). Other inert organic solvents which may be used include Cellosolve (trade mark) and diglyme. It is convenient to carry out this heating at a temperature at or near the reflux temperature of the mixture. The heating may also be carried out under pressure if desired.

According to embodiment (f) of the present process, a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group is heated with ammonia to yield a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom. This heating can be carried out by passing ammonia gas for a long period of time through a solution of the pyrimidotriazine in an inert organic solvent (e.g. a lower alkanol such as methanol or ethanol, cellosolve or diglyme) maintained at a temperature at or near the reflux temperature of the mixture. However, in a preferred procedure, the heating is carried out by treating the pyrimidotriazine with a solution of ammonia in a suitable solvent (e.g. 3-N ethanolic ammonia) and heating the mixture in a closed vessel at a temperature

of from 90°C to 110°C for 12 to 16 hours. It is preferred to use a large excess of ammonia in this embodiment.

According to embodiment (g) of the present process, a pyrimidotriazine corresponding to formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom is treated with an amine of formula VI to yield a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group. It is convenient to use at least a part of the amine of formula VI in the form of an acid addition salt thereof, particularly the hydrochloride. It is also convenient to use a molar excess (e.g. a 4—5 molar excess) of the amine or acid addition salt thereof. This treatment may suitably be carried out in an inert organic solvent, preferably a lower alkanol (e.g. methanol or ethanol) which may be aqueous in nature. Other organic solvents which are inert under the conditions employed may also be used. It is expedient to carry out this treatment at an elevated temperature, suitably at or near the reflux temperature of the mixture.

The anti-inflammatory activity of the pyrimidotriazines provided by the present invention can be demonstrated in standard tests for such activity. One such test comprises administering the pyrimidotriazine to be tested to groups of six male albino rats on each of five consecutive days. Three hours after the first administration, 0.05 ml of a 0.5% suspension of *Mycobacterium butyricum* in sterilized olive oil is injected into the right hind foot of each rat. The volume of the paw of each rat is measured immediately after administration of the pyrimidotriazine and again 96 hours later; the difference being recorded as a volume of oedema. From these measurements there is calculated the dosage required to produce a 30 percent reduction in oedema which is designated as ED<sub>30</sub>. In this test, 5 - amino - 7 - ethyl - pyrimido [5,4-e] - as - triazine has an ED<sub>30</sub> of 1.95 mg/kg *per os* and 5 - amino - 7 - methyl - pyrimido [5,4-e] - as - triazine has an ED<sub>30</sub> of 9.0 mg/kg *per os*. Phenylbutazone, a well-known anti-inflammatory agent, has an ED<sub>30</sub> of 5.1 in the same test.

The pyrimidotriazines provided by the present invention may accordingly be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. Examples of suitable carriers, which may be organic or inorganic in nature, are water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols or petroleum jelly. The pharmaceutical preparations may be made up in a dosage form suitable for enteral (e.g. oral) or parenteral administration; for example in a solid

form (e.g. as capsules, tablets, dragées or suppositories) or in a liquid form (e.g. as solutions, emulsions or suspensions). The pharmaceutical preparations may be submitted to the customary pharmaceutical techniques such as sterilization and may contain conventional pharmaceutical adjuvants such as preserving agents, stabilizing agents, wetting agents, salts for altering the osmotic pressure or buffers.

The following Examples illustrate the process provided by the invention:

#### Example 1

A) The preparation of the starting material:

127 g of 5 - amino - 4,6 - dichloro - 2 - methyl - pyrimidine were added with stirring to 465 ml of hydrazine hydrate. The internal temperature was allowed to rise spontaneously to 30°C, then the reaction vessel was cooled in an ice/salt mixture to keep the internal temperature at ca 30°C. When the exothermic phase of the reaction was almost complete, the internal temperature was allowed to rise to 35°C. The 5 - amino - 4,6 - dichloro - 2 - methyl - pyrimidine dissolved completely after ca 20 minutes and 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine was deposited from the resulting solution after seeding. The resulting mixture was stirred at room temperature for 2 hours; the solid was subsequently filtered off, washed with two 100 ml portions of cold isopropanol and two 150 ml portions of ether and dried to yield 93.5 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine of melting point 161°—163°C (with decomposition).

B) The process:

72 ml of 5-N ethanolic hydrogen chloride were added dropwise to a stirred mixture of 50 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine and 64 g of triethyl orthoformate in 250 ml of dry ethanol, the reaction temperature being maintained below 30°C by ice-cooling. The resulting pale orange suspension was stirred at room temperature for 2 hours, then the solid was filtered off and washed successively with acetone and ether to yield 62.1 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido [5,4-e] - as - triazine hydrochloride.

23.75 g of sodium bicarbonate were added to a stirred solution of 62.1 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido [5,4-e] - as - triazine hydrochloride in 1780 ml of 50% aqueous ethanol. When the effervescence has ceased, the resulting suspension of the 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido [5,4-e] - as - triazine free base was treated with 29.4 g of sodium azide, boiled under reflux for 2 hours, cooled in ice and filtered to yield 31.8 g of 5 - amino - 7 - methyl - pyrimido [5,4-e] - as - triazine having a melting point above 240°C (with de-

composition) after recrystallization from water. The thin-layer chromatogram (silica gel, 10% methanol/chloroform) showed a single spot;  $\lambda_{\max}$  (0.1-N hydrochloric acid) 218 nm ( $\epsilon=10,700$ ), 245 nm ( $\epsilon=8,000$ ), 346 nm ( $\epsilon=8,300$ ); nuclear magnetic resonance (trifluoroacetic acid):  $-0.3 \tau$  (1H, singlet),  $7.0 \tau$  (3H, singlet).

#### Example 2

- 10 In a manner analogous to that described in Example 1B, from 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine and triethyl orthoacetate there was obtained 5 - amino - 3,7 - dimethyl - pyrimido[5,4-e] - 15 *as* - triazine; melting point  $245^{\circ}$ — $246^{\circ}$ C (with decomposition);  $\lambda_{\max}$  (0.1-N hydrochloric acid) 215 nm ( $\epsilon=10,500$ ), 246 nm ( $\epsilon=8,900$ ), 350 nm ( $\epsilon=8,200$ ); nuclear magnetic resonance  $[(\text{CD}_3)_2\text{SO}]$ :  $1.53 \tau$  (2H, broad),  $7.00 \tau$  (3H, singlet),  $7.47 \tau$  (3H, singlet).

#### Example 3

- A) The preparation of the starting material:  
25 In a manner analogous to that described in Example 1A, from 5 - amino - 4,6 - dichloro - 2 - ethyl - pyrimidine there was obtained 5 - amino - 4 - chloro - 2 - ethyl - 6 - hydrazino - pyrimidine of melting point  $134^{\circ}$ — $135^{\circ}$ C.
- B) The process:  
30 In a manner analogous to that described in Example 1B, from 5 - amino - 4 - chloro - 2 - ethyl - 6 - hydrazino - pyrimidine and triethyl orthoformate there was obtained 5 - amino - 7 - ethyl - pyrimido[5,4-e] - *as* - 35 triazine; melting point  $195^{\circ}$ — $196^{\circ}$ C (with decomposition);  $\lambda_{\max}$  (0.1-N hydrochloric acid) 217 nm ( $\epsilon=10,700$ ), 244 nm ( $\epsilon=8,400$ ), 347 nm ( $\epsilon=8,000$ ); nuclear magnetic resonance  $[(\text{CD}_3)_2\text{SO}]$ :  $0.00 \tau$  (1H, singlet),  $7.11 \tau$  (2H, quadruplet),  $8.63 \tau$  (3H, triplet).

#### Example 4

- A) The preparation of the starting material:  
45 In a manner analogous to that described in Example 1A, from 5 - amino - 4,6 - dichloro - 2 - methyl - pyrimidine there was obtained 5 - amino - 4 - chloro - 2 - *n* - hexyl - 6 - hydrazino - pyrimidine.
- B) The process:  
50 In a manner analogous to that described in Example 1B, from 5 - amino - 4 - chloro - 2 - *n* - hexyl - 6 - hydrazino - pyrimidine and triethyl orthoformate there was obtained 5 - amino - 7 - *n* - hexyl - pyrimido[5,4-e] - 55 *as* - triazine; melting point  $171^{\circ}$ — $172^{\circ}$ C (with decomposition);  $\lambda_{\max}$  (0.1-N hydrochloric acid) 246 nm ( $\epsilon=8,900$ ), 347 nm ( $\epsilon=7,900$ ); nuclear magnetic resonance  $[(\text{CD}_3)_2\text{SO}]$ :  $0.06 \tau$  (1H, singlet),  $7.2 \tau$  (multiplet),  $8$ — $9.4 \tau$  (11H, multiplet).

#### Example 5

A mixture of 30 g of 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 1B) 18 g of methylamine hydrochloride, 60 ml of a 25— 65 30% (wt/vol) solution of methylamine in water and 600 ml of methanol was stirred and boiled under reflux for 5 hours, a second equal portion of methylamine solution being added after 3 hours. After standing over- 70 night, the resulting mixture was evaporated to dryness and the residue was treated with 600 ml of water, cooled in ice and filtered. The resulting solid was washed with water and dried to yield 30 g of 7 - methyl - 5 - 75 methylamino - pyrimido[5,4-e] - *as* - triazine of melting point  $271^{\circ}$ C (with decomposition). Recrystallization from *n*-butanol did not significantly change the melting point;  $\lambda_{\max}$  (0.1-N hydrochloric acid) 223 nm ( $\epsilon=12,000$ ), 253 nm ( $\epsilon=5,300$ ), 360 nm ( $\epsilon=9,900$ ); nuclear magnetic resonance (trifluoroacetic acid):  $-0.3 \tau$  (1H, singlet),  $+0.1 \tau$  (1H, broad),  $6.35 \tau$  (3H, singlet),  $7.0 \tau$  (3H, singlet). 85

#### Example 6

32.0 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido[5,4-e] - *as* - triazine hydrochloride (prepared as described in the first paragraph of Example 1B) were suspended in 1 litre of ethanol and treated with 100 ml of a 33% (wt/wt) solution of dimethylamine in ethanol. The mixture was stirred at room temperature for 20 hours. After cooling to  $0^{\circ}$ C, the crystalline solid was collected and recrystallized from *ca* 230 ml of ethanol to give 15.0 g of 5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point  $190^{\circ}$ — $191^{\circ}$ C. 90 95

The mother liquors from the treatment were combined with the mother liquors from the recrystallization and evaporated *in vacuo*. The residue was extracted with 500 ml of benzene, the benzene extract was evaporated *in vacuo* and the residue was recrystallized from *ca* 105 50 ml of ethanol to yield a further 3.35 g of 5 - diethylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point  $190^{\circ}$ — $191^{\circ}$ C.

#### Example 7

0.38 g of 5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 6) were suspended in 8 ml of methanol and 0.2 g of methylamine hydrochloride and 2 ml of a 33% (wt/wt) 110 115 solution of methylamine in ethanol were added to the suspension obtained. The mixture was heated under reflux for 2 hours and a further 2 ml of a 33% (wt/wt) solution of methylamine in ethanol were added. The heating was continued for a further 2 hours. The mixture was cooled to  $0^{\circ}$ C, the solid which separated was collected and recrystallized 120

from ca 15 ml of *n*-butanol to give 0.28 g of 5 - methylamino - 7 - methyl - pyrimido [5,4-e] - *as* - triazine of melting point 271°C (with decomposition).

#### 5 Example 8

1.1 g of 5 - chloro - 1, 2 - dihydro - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared according to the procedure described in the second paragraph of Example 1B) were suspended in 25 ml of ethanol and treated with 3 ml of a solution of 33% (wt/wt) methylamine in ethanol. The mixture was stirred at room temperature for 20 hours. The mixture was then cooled to 0°C, the resulting solid was collected and recrystallized from ca 40 ml of *n*-butanol to yield 0.45 g of 5 - methylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 271°C (with decomposition).

#### 20 Example 9

A mixture of 14.9 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine (prepared as described in Example 1A) 27.0 g of trimethyl orthobenzoate and 180 ml of dry ethanol was stirred until the bulk of the solid had dissolved. The mixture was cooled to ca 15°C in ice-water and 36.7 ml of 5-*N* ethanolic hydrogen chloride were added. The red solution was stirred for 2 hours, the cooling bath was removed after 15 minutes and 150 ml of dry ether were added after 1 hour. The red solid which formed was filtered off, washed twice with ether and dried in air to yield 25.4 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine hydrochloride.

The foregoing hydrochloride was suspended in 300 ml of water and the mixture stirred at room temperature for 1 hour. The resulting bright orange solid was filtered off, washed free from acid with several portions of water and dried in a desiccator. 17.66 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine were obtained.

A mixture of 17.6 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - 3 - phenyl - pyrimido [5,4-e] - *as* - triazine, 36.6 g of a 33% (wt/wt) solution of dimethylamine in ethanol and 300 ml of dry ethanol was stirred at room temperature overnight. The mixture was then evaporated to dryness, the residual orange solid was suspended in 100 ml of ether, filtered off, washed twice with ether and dried to give 16.4 g of crude 5 - dimethyl - amino - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine of melting point 214°—215°C.

8.0 g of the foregoing crude product were recrystallized from 120 ml of boiling methyl-Cellosolve to give 6.6 g of pure 5 - dimethylamino - 7 - methyl - 3 - phenyl - pyrimido [5,4-e] - *as* - triazine of melting point 226°—

227°C. Further recrystallization from 150 ml of boiling *n*-butanol with the addition of alumina yielded 6.2 g of the same product of melting point 226°—227°C.

#### Example 10

A mixture of 8.2 g of 5 - dimethylamino - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 9), 4.1 g of methylamine hydrochloride, 28 g of a 33% (wt/wt) solution of methylamine in ethanol and 300 ml of dry methanol was stirred and heated under reflux overnight. The mixture was evaporated to dryness and the yellow solid remaining behind was suspended in 100 ml of water, filtered off and washed twice with water. 7.4 g of product of melting point 215°—217°C were obtained. This product was dried in a desiccator and recrystallized from 200 ml of boiling methanol to yield 5.56 g of pure 7 - methyl - 5 - methylamino - 3 - phenyl - pyrimido [5,4-e] - *as* - triazine of melting point 224°—225°C.

#### Example 11

A mixture of 54.3 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - 3 - phenyl - pyrimido [5,4-e] - *as* - triazine, prepared as described in the first two paragraphs of Example 9, 21.4 g of sodium azide, 600 ml of ethanol and 600 ml of water was stirred and heated under reflux for 4 hours, the initial orange solid being replaced by a brown solid during this time. The mixture was cooled in ice for 1 hour, the brown solid was filtered off and washed twice with water and dried in a desiccator. 39.5 g of product of melting point 267°—269°C (with decomposition) were obtained. This product was recrystallized twice from 700 ml of hot (105°C) dimethylformamide to yield 30.4 g of pure 5 - amino - 7 - methyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine of melting point 269°C (with decomposition).

#### Example 12

In a manner analogous to that described in the first two paragraphs of Example 9, 5 - amino - 4 - chloro - 2 - ethyl - 6 - hydrazino - pyrimidine (prepared in accordance with Example 3A) was converted into 5 - chloro - 1,2 - dihydro - 7 - ethyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine of melting point 172°—173°C.

In a manner analogous to that described in Example 11, 5 - chloro - 1,2 - dihydro - 7 - ethyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine was converted into 5 - amino - 7 - ethyl - 3 - phenyl - pyrimido[5,4-e] - *as* - triazine of melting point 239°—240°C.

#### Example 13

A) The preparation of the starting material:  
A mixture of 38.7 g of 5 - amino - 4,6 -

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dichloro - 2 - phenyl - pyrimidine and 315 ml of hydrazine hydrate was stirred and heated to 70°C. An exothermic reaction occurred. After the spontaneous increase in temperature had ceased, the mixture was stirred at 90°C for 10 minutes and the brown solution which formed was cooled in ice. The resulting buff solid was filtered off, washed twice with water and dried in a desiccator to yield 38.5 g of product of melting point 173—174°C. Recrystallization from 1200 ml of boiling toluene with the addition of 15 g of silica gel yielded 28.6 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - phenyl - pyrimidine of melting point 178°—179°C (with effervescence).

B) The process:

A mixture of 81.6 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - phenyl - pyrimidine, 90 g of triethyl orthoformate and 1500 ml of dry ethanol was stirred and cooled in ice-water while 180 ml of 4.5-N ethanolic hydrogen chloride were added over a period of about 5 minutes. The mixture was then stirred at room temperature for a further 1.5 hours. The red-orange solid which resulted was filtered off, washed twice with ether and dried in a desiccator to yield 78.3 g of 5 - chloro - 1,2 - dihydro - 7 - phenyl - pyrimido[5,4-e] - as - triazine hydrochloride.

The foregoing hydrochloride was stirred with 1000 ml of water for 40 minutes and the orange free base was filtered off and washed with water until the filtrates were free of acid. The solid was dried in a desiccator and yielded 58.0 g of 5 - chloro - 1,2 - dihydro - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 182—184°C (with decomposition).

A mixture of 29.4 g of 5 - chloro - 1,2 - dihydro - 7 - phenyl - pyrimido[5,4-e] - as - triazine, 96 ml of a 33% (wt/wt) solution of dimethylamine in ethanol and 250 ml of dry ethanol was stirred at room temperature for 6 hours. The solid which precipitated from the solution during this time was filtered off, washed with ethanol and ether and dried to give 13.9 g of crude 5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 238°—239°C. The filtrate was left to stand overnight at 0°C and a second crop of solid was filtered off, washed twice with ethanol, twice with ether and dried in a desiccator, 10.5 g of crude 5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 237°—239°C being obtained.

The combined crude products were recrystallized from 1400 ml of boiling *n*-butanol with the addition of charcoal to give 22.3 g of pure 5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 243°—244°C. 8.0 g of this product were again recrystallized from 500 ml of boil-

ing *n*-butanol to give 7.65 g of pure product of melting point 243.5—245°C.

Example 14

A mixture of 13.6 g of 5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine (prepared as described in Example 13), 47.0 g of a 33% (wt/wt) solution of methylamine in ethanol, 7.8 g of methylamine hydrochloride and 500 ml of dry methanol was stirred and heated under reflux for 66 hours, during which time a clear orange coloured solution formed. The mixture was evaporated to dryness and the orange solid obtained was suspended in 200 ml of water, filtered off and washed twice with water. After drying, 14.0 g of crude 5 - methylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 203°—204°C were obtained. After recrystallization from 350 ml of boiling *n*-butanol, 11.1 g of pure 5 - methylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 204°—206°C were obtained.

Example 15

A mixture of 29.4 g of 5 - chloro - 1,2 - dihydro - 7 - phenyl - pyrimido[5,4-e] - as - triazine (prepared as described in the first two paragraphs of Example 13B), 12.6 g of sodium azide, 350 ml of ethanol and 350 ml of water was stirred and heated under reflux for 1 hour. The mixture was then cooled in ice for 2 hours and the brown solid was filtered off, washed twice with water and dried in a desiccator. 16.15 g of crude 5 - amino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 278°—279°C were obtained.

The foregoing crude product was recrystallized from 275 ml of boiling methylCello-solve with the addition of charcoal to give 12.4 g of pure 5 - amino - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 283°—284°C. A further recrystallization from the same solvent gave 10.2 g of the same pure product with an unchanged melting point.

Example 16

In a manner analogous to that described in the first two paragraphs of Example 13B, 5 - amino - 4 - chloro - 6 - hydrazino - 2 - phenyl - pyrimidine was converted by reaction with triethyl orthoacetate into 5 - chloro - 1,2 - dihydro - 3 - methyl - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 184°—185°C.

In a manner analogous to that described in Example 15, 5 - chloro - 1,2 - dihydro - 3 - methyl - 7 - phenyl - pyrimido[5,4-e] - as - triazine was converted into 5 - amino - 3 - methyl - 7 - phenyl - pyrimido[5,4-e] - as - triazine of melting point 243°—244°C.

Example 17

A) The preparation of the starting material:



A solution of 40 g of 5 - amino - 4,6 - dichloro - 2 - trifluoromethyl - pyrimidine and 20 ml of hydrazine hydrate in 200 ml of ethanol was stirred at room temperature for 1 hour. The mixture was evaporated to dryness *in vacuo* and the residue treated with 800 ml of ethyl acetate. The solution was dried over sodium sulphate and then evaporated *in vacuo* to an oil which subsequently crystallized. Recrystallization from 350 ml of benzene gave 34.8 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - trifluoromethyl - pyrimidine of melting point 145°—147°C.

B) The process:

A solution of 34.8 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - trifluoromethyl - pyrimidine, 34.8 g of triethyl orthoformate and 38 ml of 5-N ethanolic hydrogen chloride in 600 ml of dry ethanol was stirred at room temperature for 2 hours. The resulting red solution was evaporated to dryness *in vacuo* and the orange coloured residue washed on to a filter with petrol (boiling range 40°—60°C) and then dried. 42.0 g of 5 - chloro - 1,2 - dihydro - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine hydrochloride of melting point 184°C (with decomposition) was obtained.

A solution of 42.0 g of 5 - chloro - 1,2 - dihydro - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine hydrochloride and 87 ml of a 33% (wt/wt) solution of dimethylamine in ethanol in 100 ml of dry ethanol was stirred under nitrogen in the absence of light for 20 hours. Charcoal was then added and air was bubbled through the mixture for 1 hour. The mixture was then filtered, the filtrate evaporated to dryness *in vacuo* and the residue partitioned between 500 ml of water and 500 ml of benzene. The aqueous phase was separated and extracted four times with 300 ml of benzene each time. The combined benzene solutions were dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude product was purified by chromatography on silica gel. Recrystallization from carbon tetrachloride gave 15.9 g of 5 - dimethylamino - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine of melting point 126°—127.5°C.

Example 18

A solution of 5.5 g of 5 - dimethylamino - 7 - trifluoro - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 17), and 17 ml of a 33% (wt/wt) solution of methylamine in ethanol in 100 ml of dry methanol was boiled under reflux for 1.5 hours and then evaporated to dryness *in vacuo*. The residue was recrystallized from 1100 ml of carbon tetrachloride to yield 4.2 g of 5 - methylamino - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine of melting point 180°—182°C.

Example 19

A solution of 6.2 g of 5 - dimethylamino - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 17B) in 250 ml of dry methanol was stirred and heated at 80°C while anhydrous ammonia gas was bubbled through the solution for 2 hours. The mixture was left to stand at room temperature overnight and then evaporated to dryness *in vacuo*. The residue was recrystallized from toluene to give 3.8 g of 5 - amino - 7 - trifluoromethyl - pyrimido[5,4-e] - *as* - triazine of melting point 157°—159.5°C.

Example 20

A solution of 29 g of 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 1B), 41 g of allylamine and 43 ml of 5-N ethanolic hydrogen chloride in 490 ml of dry methanol was stirred and heated at 70°C for 24 hours, a further 10 g of allylamine being added after 19 hours. The mixture was left to stand overnight at room temperature, evaporated to dryness *in vacuo* and the residue partitioned between 250 ml of water and 500 ml of chloroform. The aqueous phase was separated and extracted with 250 ml of chloroform and then twice with 100 ml of chloroform each time. The combined chloroform solutions were dried over sodium sulphate and evaporated *in vacuo* to give 36.0 g of crude product. This was recrystallized from 800 ml of water with the addition of charcoal and yielded 25.9 g of pure 5 - allyl - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 132°—133.5°C.

Example 21

In a manner analogous to that described in Example 20, from 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine and propargylamine there was obtained 7 - methyl - 5 - propargylamino - pyrimido[5,4-e] - *as* - triazine of melting point 185°—186°C.

Example 22

In a manner analogous to that described in Example 20, from 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine and cyclopropylamine there was obtained 5 - cyclopropylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 151°—152°C.

Example 23

In a manner analogous to that described in Example 20, from 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine and ethylamine there was obtained 5 - ethylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 192.5°—194.5°C (with decomposition).

Example 24

In a manner analogous to that described

in Example 20, from 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine and isopropylamine there was obtained 5 - isopropylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 119°—121°C.

#### Example 25

In a manner analogous to that described in Example 20, from 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine and *n*-butylamine there was obtained 5 - *n* - butylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 116.5°—118°C.

#### Example 26

A) The preparation of the starting material:  
In a manner analogous to that described in Example 1A, from 5 - amino - 2 - benzyl - 4,6 - dichloro - pyrimidine there was obtained 5 - amino - 2 - benzyl - 4 - chloro - 6 - hydrazino - pyrimidine of melting point 132°—136°C (with decomposition).

#### B) The process:

In a manner analogous to that described in the first paragraph of Example 17B, 5 - amino - 2 - benzyl - 4 - chloro - 6 - hydrazino - pyrimidine was converted into 7 - benzyl - 5 - chloro - 1,2 - dihydro - pyrimido[5,4-e] - *as* - triazine hydrochloride of indefinite melting point 175°—185°C (with decomposition).  
11.4 g of a 33% (wt/wt) solution of dimethylamine in ethanol were added at room temperature to a suspension of 4.8 g of 7 - benzyl - 5 - chloro - 1,2 - dihydro - pyrimido[5,4-e] - *as* - triazine hydrochloride in 100 ml of ethanol. The mixture was then stirred at room temperature. A solution formed initially and then a crystalline solid precipitated. After stirring the mixture for 17 hours, the yellow crystals were collected and recrystallized from ethyl acetate. 1.77 g of 7 - benzyl - 5 - dimethylamino - pyrimido[5,4-e] - *as* - triazine of melting point 158—160°C were obtained.

#### Example 27

72 ml of 5-*N* ethanolic hydrogen chloride were added dropwise to a stirred mixture of 50 g of 5 - amino - 4 - chloro - 6 - hydrazino - 2 - methyl - pyrimidine and 64 g of triethyl orthoformate in 250 ml of dry ethanol, the reaction temperature being maintained below 30°C by ice-cooling. The resulting pale orange suspension was stirred at room temperature for 2 hours, then the solid was filtered off and washed successively with acetone and ether to yield 62.1 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido[5,4-e] - *as* - triazine hydrochloride.

11 g of 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido[5,4-e] - *as* - triazine hydrochloride were suspended in 300 ml of absolute ethanol, the mixture was stirred and

22 g of morpholine were added. The mixture was then stirred at room temperature for 15 hours. The precipitated solid was filtered off and the filtrate was evaporated *in vacuo*. The residue was extracted three times with 100 ml of benzene each time, the benzene extracts were evaporated to dryness and the residue was combined with the solid initially collected. Recrystallization from 300 ml of ethanol yielded 6.8 g of 7 - methyl - 5 - morpholino - pyrimido[5,4-e] - *as* - triazine of melting point 207°—209°C.

#### Example 28

1 g of 5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 6) was added to a solution of 1.9 g of hydroxylamine in 40 ml of methanol. The resulting solution was heated under reflux for 2 hours. The mixture was cooled and the resulting solid was collected. Recrystallization from 50 ml of water gave 0.45 g of 5 - hydroxylamino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine of melting point 265°—270°C (with decomposition).

#### Example 29

In a manner analogous to that described in the first paragraph of Example 27, 5 - chloro - 1,2 - dihydro - 7 - ethyl - pyrimido[5,4-e] - *as* - triazine hydrochloride was prepared from 5 - amino - 4 - chloro - 2 - ethyl - 6 - hydrazino - pyrimidine.

3.34 g of 5 - chloro - 1,2 - dihydro - 7 - ethyl - pyrimido[5,4-e] - *as* - triazine hydrochloride were taken up in 30 ml of dry methanol and 3 ml of ethanolamine were added. The mixture was stirred vigorously at room temperature for 22 hours. The mixture was filtered and the filtrate evaporated. A dark coloured residue remained and this was dissolved in chloroform containing 5% (vol/vol) methanol and chromatographed on alumina. A broad yellow band was eluted with chloroform containing 5% (vol/vol) methanol. The eluate was evaporated to give 1.8 g of a crystalline solid which, after recrystallization from ethyl acetate, yielded yellow crystals of 7 - ethyl - 5 - (2 - hydroxy - ethylamino) - pyrimido[5,4-e] - *as* - triazine of melting point 153°—154°C.

#### Example 30

0.8 g of 5 - amino - 7 - methyl - pyrimido[5,4-e] - *as* - triazine (prepared as described in Example 1B) was taken up in 8 ml of glacial acetic acid and 4 ml of acetic anhydride and the mixture was heated at 100°C for 15 minutes. On cooling the solution, 0.44 g of crystals was deposited. These crystals were collected and washed with ethanol and ether and, after drying melted at 184°—185°C (with decomposition). Two recrystallizations from anhydrous ethanol gave 0.28 g of 5 - acetamido - 7 - methyl - pyrimido[5,4-e] -

as - triazine in the form of red needles of melting point 185°—186°C (with decomposition).

#### Example 31

- 5 0.8 g of 5 - amino - 7 - methyl - pyrimido [5,4-e] - as - triazine was taken up in 10 ml of propionic anhydride and the mixture heated at 80°C for 30 minutes. On cooling, fine red crystals of melting point 154°—155°C were deposited and were collected and washed with ether. After recrystallization from anhydrous ethanol, 0.57 g of 7 - methyl - 5 - propionamido - pyrimido[5,4-e] - as - triazine of melting point 156°C was obtained.

#### Example 32

- 15 8.0 g of 5 - amino - 7 - methyl - pyrimido [5,4-e] - as - triazine were taken up in 12 ml of isobutyric anhydride, 11 ml of triethylamine and 180 ml of chloroform and the mixture was stirred and heated under reflux for 5 hours. The solution was cooled, a small amount of solid was filtered off and the filtrate was evaporated *in vacuo*. The residual red solid was recrystallized from anhydrous ethanol to give 4.6 g of 5 - isobutyramido - 7 - methyl - pyrimido[5,4-e] - as - triazine in the form of orange-red needles of melting point 157.5°—159°C.

#### Example 33

- 30 4.0 g of 5 - amino - 7 - methyl - pyrimido [5,4-e] - as - triazine were taken up in 45 ml of absolute pyridine and, with vigorous stirring, 4.5 ml of *p* - chloro - benzoyl chloride were added dropwise over a period of 1 minute. The mixture was stirred for 10 minutes and 150 ml of water were added to the resulting solution. A solid precipitated and this was collected and washed with water and acetone. The solid was then dissolved in chloroform containing 10% (vol/vol) methanol and, after filtering the solution, petrol of boiling range 60°—80°C was added. 2.75 g of a red crystalline deposit, 5 - (*p* - chloro - benzamido) - 7 - methyl - pyrimido[5,4-e] - as - triazine of melting point 203°C (with decomposition) were obtained.

#### Example 34

- 50 In a manner analogous to that described in Example 6, from 5 - chloro - 1,2 - dihydro - 7 - methyl - pyrimido[5,4-e] - as - triazine and diethylamine there was obtained 5 - diethylamino - 7 - methyl - pyrimido [5,4-e] - as - triazine of melting point 123°C.

#### Example 35

- 55 In a manner analogous to that described in Example 6, 5 - chloro - 1,2 - dihydro - 7 - neopentyl - pyrimido[5,4-e] - as - triazine hydrochloride was converted into 5 - dimethylamino - 7 - neopentyl - pyrimido [5,4-e] - as - triazine of melting point 187°—188.5°C.

#### Example 36

In a manner analogous to that described in Example 7, 5 - dimethylamino - 7 - neopentyl - pyrimido[5,4-e] - as - triazine was converted into 5 - methylamino - 7 - neopentyl - pyrimido[5,4-e] - as - triazine of melting point 162°—163°C.

The following Examples illustrate typical pharmaceutical preparations containing the pyrimidotriazines provided by the present invention.

#### Example A

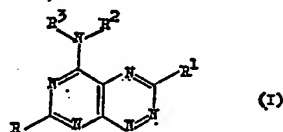
25.0 g of 7 - methyl - 5 - methylamino - pyrimido[5,4-e] - as - triazine are mixed with 150 g of lactose and 30 g of starch and the mixture is passed through a comminuting machine. The mixture is then returned to the mixer and 5 mg of talc are added, whereupon the entire mixture is blended thoroughly and finally filled into opaque hard-shell gelatin capsules. Each capsule contains 210 mg of ingredients with an active ingredient content of 25 mg.

#### Example B

Capsules are prepared in the manner described in Example A using 5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine or 5 - methylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine in place of 7 - methyl - 5 - methylamino - pyrimido [5,4-e] - as - triazine.

#### WHAT WE CLAIM IS:—

1) Pyrimidotriazines of the general formula



wherein R represents a trifluoromethyl, lower alkyl, aryl or lower aralkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl, aryl or lower aralkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl, hydroxy, hydroxy-(lower alkyl) or acyl group or R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group which may be joined directly or through an oxygen, nitrogen or sulphur atom to form with the nitrogen atom to which they are attached a 5-membered or 6-membered heteromono-cyclic ring.

2) Pyrimidotriazines of formula I given in claim 1, wherein R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydrogen atom or a lower alkyl group.

3) Pyrimidotriazines of formula I given in claim 1, wherein R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group.

4) Pyrimidotriazines as claimed in any one of claims 1 to 3 inclusive, wherein R represents a methyl or ethyl group.

5) Pyrimidotriazines as claimed in any one of claims 1 to 4 inclusive, wherein R<sup>1</sup> represents a hydrogen atom.

6) Pyrimidotriazines as claimed in any one of claims 1 to 5 inclusive, wherein R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a methyl group or R<sup>2</sup> and R<sup>3</sup> each represent a methyl group.

7) Pyrimidotriazines of formula I given in claim 1, wherein R represents other than a lower alkyl group when R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydrogen atom or a lower alkyl group or R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group.

8) 7 - Methyl - 5 - methylamino - pyrimido[5,4-c] - as - triazine.

9) 5 - Dimethylamino - 7 - methyl - pyrimido[5,4-c] - as - triazine.

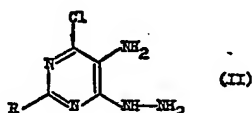
10) 5 - Ethylamino - 7 - methyl - pyrimido[5,4-c] - as - triazine.

11) 5 - Methylamino - 7 - phenyl - pyrimido[5,4-c] - as - triazine.

12) 5 - Dimethylamino - 7 - phenyl - pyrimido[5,4-c] - as - triazine.

13) A process for the manufacture of the pyrimidotriazines of formula I in claim 1, which process comprises

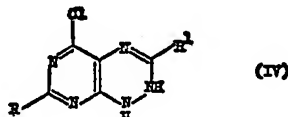
(a) reacting a hydrazinopyrimidine of the general formula



wherein R has the significance given in claim 1, with a compound of the general formula



wherein R<sup>1</sup> has the significance given in claim 1 and R<sup>4</sup> represents a lower alkyl group, in the presence of a strong acid to give an acid addition salt of a compound of the general formula



wherein R and R<sup>1</sup> have the significance given

in claim 1, and treating said acid addition salt or the free base obtained therefrom with ammonia under oxidising conditions or with an alkali metal azide or with ammonia in the presence of an alkali metal azide to give a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom, or

(b) reacting an acid addition salt of a compound of formula IV or the free base obtained therefrom with an amine of the general formula



wherein R<sup>20</sup> represents a hydrogen atom and R<sup>30</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group or R<sup>20</sup> and R<sup>30</sup> each represent a lower alkyl group which may be joined directly or through an oxygen, nitrogen or sulphur atom to form with the nitrogen atom to which they are attached a 5-membered or 6-membered heteromonocyclic ring, under oxidising conditions to give a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> have any of the values according to R<sup>20</sup> and R<sup>30</sup> earlier in this claim, or

(c) treating a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group with hydroxylamine to give a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a hydroxy group, or

(d) appropriately acylating a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom to give a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents an acyl group, or

(e) converting a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a methyl group into a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group by heating with an amine of the general formula



wherein R<sup>21</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group, or

(f) converting a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a

methyl group into a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom by heating with ammonia, or

- 5 (g) treating a pyrimidotriazine of formula I in which R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom with an amine of formula VI given earlier in this claim to yield a pyrimidotriazine of formula I in which R<sup>2</sup> represents a  
10 hydrogen atom and R<sup>3</sup> represents a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, lower aralkyl or hydroxy-(lower alkyl) group.

- 14) A process according to claim 13,  
15 wherein a hydrazinopyrimidine of formula II in which R represents a lower alkyl group is reacted with a compound of formula III in which R<sup>1</sup> represents a hydrogen atom or a lower alkyl group in the presence of a  
20 strong acid to give an acid addition salt of a compound of formula IV in which R represents a lower alkyl group and R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and said acid addition salt or the free base  
25 obtained therefrom is treated with an alkali metal azide to give a pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and R<sup>2</sup> and R<sup>3</sup> each  
30 represent a hydrogen atom, or a pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and R<sup>2</sup> and R<sup>3</sup> each represent a hydrogen atom is treated with  
35 an amine of formula IV in which R<sup>21</sup> represents a lower alkyl group to yield a pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower  
40 alkyl group.

- 15) A process according to claim 13, wherein a hydrazinopyrimidine of formula II in which R represents a lower alkyl group  
45 is reacted with a compound of formula III in which R<sup>1</sup> represents a hydrogen atom or a lower alkyl group in the presence of a strong acid to give an acid addition salt of a compound of formula IV in which R represents a lower alkyl group and R<sup>1</sup> represents a  
50 hydrogen atom or a lower alkyl group and said acid addition salt or the free base obtained therefrom is reacted with an amine of formula V in which R<sup>20</sup> represents a hydrogen atom and R<sup>30</sup> represents a lower alkyl group or  
55 R<sup>20</sup> and R<sup>30</sup> each represent a lower alkyl group under oxidising conditions to give a pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl group or R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group, or a

pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower alkyl group and R<sup>2</sup> and R<sup>3</sup> each represent a methyl group is converted into a pyrimidotriazine of formula I in which R represents a lower alkyl group, R<sup>1</sup> represents a hydrogen atom or a lower  
70 alkyl group, R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a lower alkyl group by heating with an amine of formula VI in which R<sup>21</sup> represents a lower alkyl group.

16) A process according to any one of  
75 claims 13 to 15 inclusive, wherein there is manufactured a pyrimidotriazine of formula I in which R represents a methyl or ethyl group.

17) A process according to any one of  
80 claims 13 to 16 inclusive, wherein there is manufactured a pyrimidotriazine of formula I in which R<sup>1</sup> represents a hydrogen atom.

18) A process according to any one of  
85 claims 13 to 17 inclusive, wherein there is manufactured a pyrimidotriazine of formula I in which R<sup>2</sup> represents a hydrogen atom and R<sup>3</sup> represents a methyl group or R<sup>2</sup> and R<sup>3</sup> each represent a methyl group.

19) A process according to claim 13,  
90 wherein there is manufactured a pyrimidotriazine of formula I in which R represents other than a lower alkyl group when R<sup>1</sup> represents a hydrogen atom or a lower alkyl group, R<sup>2</sup> represents a hydrogen atom and  
95 R<sup>3</sup> represents a hydrogen atom or a lower alkyl group or R<sup>2</sup> and R<sup>3</sup> each represent a lower alkyl group.

20) A process according to claim 13, claim  
100 14 or any one of claims 16 to 18 inclusive, wherein 7 - methyl - 5 - methylamino - pyrimido[5,4-e] - as - triazine is manufactured.

21) A process according to claim 13, claim  
105 15 or any one of claims 16 to 18 inclusive, wherein 5 - dimethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine is manufactured.

22) A process according to claim 13, claim  
110 14, claim 16 or claim 17, wherein 5 - ethylamino - 7 - methyl - pyrimido[5,4-e] - as - triazine is manufactured.

23) A process according to claim 13 or  
115 claim 19, wherein 5 - methylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine is manufactured.

24) A process according to claim 13 or  
120 claim 19, wherein 5 - dimethylamino - 7 - phenyl - pyrimido[5,4-e] - as - triazine is manufactured.

25) A process for the manufacture of the  
pyrimidotriazines of formula I given in claim 1, substantially as hereinbefore described in any one of Examples 1 to 4.

26) A process for the manufacture of the  
125 pyrimidotriazines of formula I given in claim 1, substantially as hereinbefore described in any one of Examples 6 to 8.

- 27) A process for the manufacture of the pyrimidotriazines of formula I given in claim 1, substantially as hereinbefore described in any one of Examples 9 to 22 and 26 to 33.
- 5 28) A process for the manufacture of the pyrimidotriazines of formula I given in claim 1 substantially as hereinbefore described in any one of Examples 5, 23 to 25, and 34 to 36.
- 10 29) Pyrimidotriazines of formula I given in claim 1, when manufactured by the process claimed in any one of claims 13 to 28 inclusive.
- 30) A pharmaceutical preparation containing a pyrimidotriazine of formula I given in claim 1 in association with a compatible pharmaceutical carrier. 15

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